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Nighttime road traffic noise exposure at the least and most exposed façades and sleep medication prescription redemption - a Danish cohort study

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Abstract

Study Objectives Traffic noise has been associated with poor sleep quality and short sleep duration. This study investigates the association between nighttime road traffic noise at the least and most exposed façade of the residence, and redemption of sleep medication.

Methods In a cohort of 44,438 Danes, aged 50-64 at baseline (1993-97), we identified all addresses from 1987-2015 from a national registry, and calculated nighttime road traffic noise at the most and least exposed façades. Using Cox Proportional Hazard Models we investigated the association between residential traffic noise over 1, 5 and 10 years before redemption of the first sleep medication prescription in the Danish National Prescription Registry. During a median follow-up time of 18.5 years, 13,114 persons redeemed a prescription.

Results We found that 10-year average nighttime exposure to road traffic noise at most exposed façade was associated with a hazard ratio (HR) of 1.05, 95 % confidence interval (CI) (1.00-1.10) for $L_n > 55$ as compared to ≤ 45 dB, which when stratified by sex was confined to men (HR 1.16, 95 % CI 1.08-1.25). For the least exposed façade the HR for $L_n > 45$ vs. ≤ 35 dB was 1.00, 95 % CI (0.95-1.05). For the most exposed façade, the overall association was strongest in smokers and physically inactive.

Conclusion Long-term residential nighttime noise exposure at the most exposed façade may be associated with a higher likelihood of redeeming prescriptions for sleep medication, especially among men, smokers, and physically inactive.

Keywords: Cohort study; sleep medication; prescription registry; road traffic noise; epidemiology

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Statement of Significance

The quality of the evidence for an association between traffic noise and sleep has been evaluated as very low to moderate by a WHO expert group; emphasizing the need for more prospective studies. This prospective cohort study investigated residential traffic noise at the least and most exposed façade in relation to sleep medication prescriptions; finding a positive association between 10-year average noise level at the most exposed façade, especially for men, but no association for the least exposed façade. The study contributes substantially to the evidence-base on traffic noise and sleep, given its numerous cases and its noise modelling at both the least and most exposed façade. The finding of differing associations across subgroups, however, warrants further investigation into this.

Introduction

According to the World Health Organization (WHO), one in five EU citizens report experiencing sleep disturbance due to nighttime traffic noise,[1] and sleep disturbance is a main health burden associated with environmental noise.[2] Traffic noise has been associated with both poorer sleep quality, as well as shorter sleep duration.[1, 3, 4]

Effects of transportation noise on sleep was evaluated in a recent systematic review commissioned by the WHO. The review included both objectively and subjectively measured sleep disturbance, and found a significant, positive association between traffic noise (road, rail, and aircraft) and objective sleep-measures using polysomnographic data, which is considered the gold standard in sleep measurement. But the authors commented that the number of studies included were few ($n = 4$) and had a low generalizability, as they were primarily conducted with young and healthy subjects. In the meta-analysis of subjectively measured sleep-disturbance based on questionnaires, they discerned between those studies asking about sleep disturbance from a specific noise source, and those not doing so. They found that when asking about a specific noise source, there was a statistically significant, positive association between transportation noise (both from aircraft, road and rail) and sleep disturbance, whereas when the noise source was not mentioned in the question, the association was still positive, but less pronounced and non-significant. A general limitation of the studies on subjectively measured sleep disturbance was the various wording and definition of questions as well as the definition of the outcome, which included both awakenings, difficulty falling asleep, and difficulty in relation to sleep maintenance.[5] The WHO expert group evaluated

the quality of the existing evidence for an association between traffic noise and the different sleep outcomes as very low to moderate,[5] emphasizing the need for future studies, especially of prospective design.

This highlights the challenges in existing studies on traffic noise and sleep, as objective sleep measurement by polysomnography is expensive and time-consuming in large studies, whereas subjective assessment of sleep quality and quantity may be affected by question wording and personal interest.[6] In order to limit such misclassification, registry-based information on prescription of sleep medication may be used as an objective measure of sleep disturbance. Three previous studies have examined the association between traffic noise and registry-based information on sleep medication prescription redemption,[7-9] with none finding an association in the main analysis, but two suggesting a positive association in subgroups defined by season and window-opening habits[7] and area-level social deprivation,[8] respectively. However, two of the studies looked at sleep medication in combination with anxiolytics and antidepressants,[8, 9] and thus further studies are required.

When studying residential traffic noise exposure, there is an increasing interest in the potentially compensatory effects of having access to a quiet side of the dwelling, which has been suggested to mitigate the harmful effects of the noise at the most exposed façade.[10-12] This is particularly relevant in studies on sleep outcomes, as having access to a quiet side would allow for alteration of night-time noise-exposure by placing the bedroom there, reflecting a behavioral regulation of noise exposure.

The aim of our study was to investigate the association between modelled nighttime road traffic noise at the most and least exposed façade of the residence, and registry-based information on redemption of sleep medication, in the Danish Diet, Cancer and Health cohort. Furthermore, we investigated potential effect modification of the association by sex, lifestyle factors and cohabitation.

Methods

Study population

A detailed description of the Diet, Cancer and Health cohort has been published previously.[13] Briefly, 160,725 Danes were invited to participate from 1993-97. Inclusion criteria were residence in the greater Copenhagen or Aarhus area, 50-64 years of age, and no previous cancer diagnosis in the Danish Cancer Registry. In total, 57,053 participants (29,875 women) accepted, and were included in the study; representing 7% of the Danish population in this age-group. The study was approved by the local ethical committees of Copenhagen and Frederiksberg Municipalities. All participants provided written informed consent, and the study was conducted according to the Helsinki Declaration.

Exposure assessment: Traffic noise

A complete residential address history for all participants was collected from July 1st, 1987 and until end of follow-up through the Danish civil registration system.[14] Road traffic noise exposure was calculated for the years 1995, 2000, 2005, 2010 and 2015, as the equivalent continuous A-weighted sound pressure level (L_{aeq}), at both the most and least exposed facade of the address during the nighttime (L_n ; 10PM-7AM).

Using SoundPLAN (version 8.0; SoundPLAN Nord ApS), which implements the joint Nordic prediction method,[15] we calculated road traffic noise exposure. This allows for calculation of equivalent noise levels for each address, based on information on traffic and topographic parameters. Initially, a three-dimensional model was built, which included building polygons (linked with address points), roads, and terrain for each year. Input variables on traffic data, vehicle distribution, diurnal variation, traffic speeds, and noise barriers, and finally noise levels were estimated and linked to each address point, and added into the model.

Information on the three-dimensional building polygons and geographic situation of all buildings in Denmark, was obtained from the Agency for Data Supply and Efficiency for the year 2012. All residential addresses within these buildings, were obtained from the Building and Housing Registry (BBR) for the year 2017.[16] For ground level dwellings, the height at which the noise was estimated was set to two meters. For all other floors, the height was calculated using the following formula: calculation height = $2 + 2.8 * (\text{number of floors} - 1)$. Buildings with an area of less than 40 m² were excluded from the noise model. Noise levels were calculated at the center of all facades of each residential building unit, and afterwards the least and most exposed facades of each residential unit was selected. In large blocks of apartments and town houses there were often several address points inside the same building polygon. To control for this, buildings with more than two address points were divided into separate building polygons for each address point. The reflection loss for building facades was set to one dB, and first and second order reflections were accounted for.

Information on terrain was downloaded from GeoDanmark[17] for the year 2012, and added to the model, to account for the screening effect from terrain. Urban areas, road surfaces, and large bodies of water were assumed fully reflecting, and all other areas were considered fully absorbent. The screening effect of buildings and noise barriers around all state roads were included. Furthermore, screening effects from noise berms, terrain, and embankments were included.

All traffic information was obtained from an updated national road and traffic database.[18] This database includes all necessary road and traffic information for air quality and noise exposure calculations. The database was an extension and update of the Danish national GIS-based road network and traffic database for 1960-2005 to the years 2005-2020. The original road network has been extended with new motorway sections that have been established since the original road network from 2007. The development in traffic flow and vehicle mix has been analysed based on traffic data from the Danish Road Directorate to estimate the trend for different road types from 1995 to 2020 as 1995 is the baseline year of the original road and traffic database.

For all road lines, the following attributes were used: road type, annual average daily traffic (AADT), vehicle distribution, and traffic speed for each of the five-year intervals, and these were added into the model.

Roads were classified in four categories: motorways and expressways, other roads with a width > 6 meters, roads with a width of 3-6 meters, and other residential roads. We assumed that for smaller roads with an AADT ≤ 200 this had no significant contribution to the noise estimation. In the the national road and traffic database, all roads with no traffic information or with traffic flows less than 200 AADT have been assigned the value 200. Information on the nighttime traffic was included based on standard diurnal traffic distributions defined in the national road and traffic database to be able to calculate hourly values for each hour during a year. Standard diurnal traffic distributions are defined for different road types (defined above), vehicle categories (passenger cars, vans, trucks, buses) and day cases (Mondays to Thursdays, Fridays, Saturdays and Sundays, and further into the holiday month of July and other months). The vehicle distribution was assessed separately for motorways and other roads as an average percentage distribution, subdivided into motorways and all other roads, and for light and heavy vehicles, respectively. Traffic speeds for each road segment are based on a combination of road type, and speed limits for each road type.

Outcome assessment: Redemption of sleep medication

Information on redeemed prescriptions for sleep medication was collected from the Danish National Prescription Registry, which contains data on all prescription drugs sold in Denmark since 1995[19]. The register includes date of dispensing as well as information on the name and type of drug prescribed according to the Anatomic Therapeutic Chemical (ATC) system.[20] However, the indication for prescribing is not available, and neither is information on prescriptions that were issued, but never redeemed. We used these data to identify people who redeemed

prescriptions for orally administered sleep medication (ATC: N05CC-CF, N05CH except N05CD08).

We excluded all participants who filed one or more prescriptions of the above-mentioned ATC-codes before start of follow-up (July 1st, 1997) in order to include only incident cases.

Covariates

At baseline of the Diet, Cancer and Health study, all participants filled in a food frequency and a lifestyle questionnaire, and anthropometric measures were collected by trained personnel. The data on diet and lifestyle factors hail from this questionnaire.[13]

Information on socioeconomic variables, e.g. highest attained education, income and marital status at baseline was available from Statistics Denmark. Selection of covariates was done *a priori*, based on a review of existing literature, biological plausibility, and availability of data, as well as a Directed Acyclic Graph (DAG) (Supplementary figure s1).

Definition of the neighborhood-level socioeconomic variables (proportion of inhabitants with low disposable income, only basic education, and unemployed at parish-level) are described in detail previously.[21]

Calculation of HRs for redemption of sleep medication was conducted in a stepwise process: First, with adjustment for age (by design), calendar year and sex (Model 1), and then additionally for socio-economic factors: educational level (basic, vocational, higher), disposable income (in quintiles), and proportion of inhabitants with low disposable income (parish level), proportion of inhabitants with only basic education (parish level), proportion of inhabitants being unemployed (parish level) (Model 2).

Lifestyle-factors were identified as mediators and not confounders in the DAG. Previous studies have proposed an association between traffic noise and several lifestyle-factors including obesity,[22-24] alcohol intake,[25] smoking,[25] and physical activity.[26, 27] Hence, adjustment for these could result in over-adjustment with removal of part of the causal pathway between traffic noise exposure and sleep medication redemption. They were thus only investigated as potential effect modifiers in interaction analyses.

Finally, information on Charlson comorbidity Index[28] one year before first prescription redemption was calculated based on data from the Danish National Patient Registry,[29] and investigated as a potential effect modifier.

Statistical methods

We used Cox Proportional Hazard Models to estimate Hazard Ratios (HR) and 95% confidence intervals (CI) for the association between residential nighttime road traffic noise exposure and redemption of sleep medication. Age was used as the underlying time scale to ensure comparison of individuals at the same age. We used left truncation at age at July 1st, 1997 to ensure at least 10 years of exposure history for all participants, and right censoring at age of prescription redemption, death, emigration, or December 31st, 2015, whichever came first.

Exposure to residential nighttime road traffic noise was modeled as time-weighted averages for the preceding 1, 5, and 10-years at a given age, taking into account preceding and current addresses in the respective periods. These exposure measures were entered as time-dependent variables into the statistical model.

The assumption of linearity of road traffic noise and continuous covariates (proportion of inhabitants with low disposable income, proportion of inhabitants with only basic education, proportion of unemployed inhabitants, alcohol intake) in relation to sleep medication redemption was evaluated by graphical evaluation using linear spline models, and the exposure-response function was plotted using smoothed splines with four degrees of freedom.[30] We found that the association between nighttime road traffic noise at both the least and most exposed façade and sleep medication redemption deviated significantly from linearity, and therefore, all analyses were performed as categorical analyses. For nighttime road traffic noise at the most exposed façade, the categories were $L_n \leq 45$ dB, $>45-50$ dB,

>50-55 dB, and >55 dB, and for the least exposed façade they were $L_n \leq 35$ dB, >35-40 dB, >40-45 dB, and >45 dB. These cutoffs for the most exposed façade were selected to reflect the WHO recommendation of reducing nighttime road traffic noise (L_n) to below 45 dB[31].

Furthermore, for one covariate, the proportion of inhabitants with low disposable income, we also found a statistically significant deviation from linearity. Hence, this was included as a spline with boundary at 0.065. The proportional hazards assumption of the Cox Models was tested by a correlation test between the scaled Schoenfeld residuals and the rank order of event time. We used the function `cox.zph` in the statistical software R, and the `proc lifetest` option in SAS. Deviation from the assumption was detected for disposable income, and thus this was included in the analyses as strata.

In order to assess potential effect modification of the association between nighttime traffic noise exposure and sleep medication redemption by sex, lifestyle-factors, and cohabitation, we conducted analyses stratified into sub-groups defined by each variable, and examined the association between nighttime road traffic noise exposure and sleep medication redemption individually in each subgroup.

Furthermore, as a sensitivity-analysis, we repeated the main analysis in a limited study population; excluding cases who had a Charlson score > 0 in the last year before first prescription redemption, as disease may be caused by traffic noise, and at the same time diagnosis of a severe disease could acutely affect the sleep quality.

All tests were based on the likelihood ratio test statistic. Two-sided 95% CI were calculated based on Wald's test of the Cox regression parameter, i.e. on the log ratio scale. P-values <0.05 were considered statistically significant. The analyses were performed using the procedure PHREG in SAS, version 9.3 on a windows platform (SAS Institute Inc., Cary, NC). The graphical evaluation of the proportional hazards assumption and the linear spline models was conducted in R, version 3.5.1.

Results

Of the 57,053 participants in the Diet Cancer and Health cohort, we excluded 574 with a cancer diagnosis before baseline, 7,792 persons who redeemed a prescription for sleep medication before baseline, 234 who emigrated or died before July 1st 1997, 1,195 persons with missing exposure-data, due to lack of address history, and 2,820 with missing covariate data; leaving 44,438 persons in the final study population. Of these, 13,114 redeemed a sleep medication prescription within the study period.

Across increasing nighttime noise exposure at the most exposed façade, the proportion of females were higher, the participants were somewhat older, there was a lower proportion of persons in the highest income quintile, and fewer who had a higher education, were cohabiting, were never or former smokers, and who were physically active. In contrast, there was a higher proportion of alcohol abstainers across increasing nighttime noise exposure. For the area-level variables, there was a higher proportion of persons with low income and of unemployed across the exposure spectrum (**Table 1**). Across increasing nighttime exposure at the

least exposed façade, there was a similar tendency of a higher proportion of females, a higher median age, and fewer with a higher education across the exposure spectrum, whereas there was no clear tendency for personal income, cohabitation, smoking status, alcohol, physical activity and area-level variables (**Table s1**). The correlation (R_{Spearman}) between noise at the least and most exposed façade was 0.46.

The association between 1, 5 and 10 year nighttime road traffic noise exposure at the most exposed façade and prescription redemption is shown in **Table 2**. There was no association with 1- and 5-year exposure, but for 10-year exposure, there was a positive tendency across exposure groups, with increasing HRs, reaching a HR (95% CI) of 1.05 (1.00-1.10) in the $L_n > 55$ dB exposure group.

In **Table 3** the associations between 1-, 5- and 10-year nighttime road traffic noise exposure at the least exposed façade and prescription redemption are shown. Here, we found a suggestion of an inverse association between traffic noise exposure and sleep medication prescription redemption over a 1- and 5-year period, in the highest exposure group ($L_n > 45$ dB) for both 1 year (HR (95 % CI): 0.95 (0.90-1.00)) and 5 years (0.96 (0.91-1.01)). However, we did not see a tendency across the exposure groups.

When investigating whether sex, lifestyle-factors, cohabitation, and education modified the association between nighttime road traffic noise at the most exposed façade and redemption of sleep medication, we found a positive association

between noise exposure and redemption of sleep medication for men, with an exposure-response association across exposure-categories, whereas for women this was not the case: For the most exposed ($L_n > 55$ dB) compared to the least exposed ($L_n \leq 45$ dB) over a 10-year period, the HR (95% CI) for men was 1.16 (1.08-1.25) and for women 0.97 (0.91-1.04). Albeit less pronounced, the results also suggested stronger positive associations and an exposure-response association between noise exposure and prescription redemption among ever vs. never smokers and non-participants in sports compared to physically active, and to some degree also for those living alone compared to those cohabiting (**Table 4**). In analyses of the least exposed façade, there were similar tendencies for sex and physical activity, albeit much less pronounced. There were also indications of a direct effect among those drinking alcohol below the recommendations, however, with no clear pattern of an exposure-response association (**Table 5**).

When examining exposure at the least and most exposed façade in combination, we found no tendency towards a combined effect of the exposure at the two facades and sleep medication prescription redemption (**Table s2**).

As a sensitivity analysis, we excluded cases with comorbidities, defined as a Charlson score > 0 ($n = 3,124$). For both facades, the HRs then suggested no association (**Table s3**).

Finally, all analyses were also calculated for road traffic noise exposure over the entire day (L_{den}), yielding very similar HRs to the findings for L_n , due to the very high

correlation (R_{Spearman} 0.999 for both least and most exposed façade) between these two measures (results not shown).

Discussion

In the present study, we found suggestions of a positive association between 10-year nighttime traffic noise exposure at the most exposed façade and redemption of sleep medication prescriptions, which in sex-stratified analyses were confined to men. We also found indications of stronger positive associations and a tendency across exposure-groups among ever smokers and non-participants in leisure-time sports, compared to never smokers and those engaging in leisure-time sports. In contrast, nighttime exposure at the least exposed façade seemed inversely associated with sleep medication prescription redemption in 1- and 5-year exposure windows, however, only in the highest exposure-category, and with no clear tendency across the lower exposure-groups. Combinations of exposure at the least and most exposed façade did not produce a clear picture of joint effects, and exclusion of those with comorbidities the last year before redemption provided HRs close to 1.00.

The strengths of the study include the large cohort size, long follow-up time, as well as a high number of cases. Furthermore, the Danish National Prescription Registry, from which the outcome data hails, is well-validated and considered both complete and of high quality, and sleep medications drugs are only available on prescription in Denmark.[32, 33] However, as the registry only runs from 1995, exclusion of persons with redemption of the included ATC-codes before study start (July 1st, 1997) in order to include incident cases only, may not be complete. We were able to follow up all participants through validated Danish registries on vital status, and had access

to detailed address history over the entire study period, which allowed calculation of average exposure over different time-windows. The modelling of exposure over time is an important study strength, as few studies have previously investigated the association in detail. The Nordic Prediction Model, which was used to calculate exposure, has been the standard method for estimation of traffic noise in the Nordic countries for many years.[15] A validation of the model, based on a number of measurements up to 300 m from the road, found the average difference between measurements and calculations to be 0.2 dB (noise from road traffic is typically within the range of 40-80 dB), showing that the model is very accurate.[15, 34]

The study limitations include the reliance on registry-based information on sleep medication prescription redemption, which prevents direct investigation of non-clinical sleep disturbance. Our study only captures more severe and persistent sleep problems, where people both contact their physician, and qualify for a prescription. The proportion of sleep medication prescription redeemers in the present cohort was 29.5 % over a median follow-up period of 18.5 years. In a National Danish health survey including 175,000 Danes, 46 % reported having experienced sleep problems within the last two weeks,[35] suggesting that we do indeed fail to capture the entire spectrum of sleep disturbances. Our findings should thus not be generalized to non-clinical sleep disturbances as a result of traffic noise, as the outcome sensitivity is reduced and information on non-clinical sleep disturbance and unredeemed prescriptions is lacking. Also, the study population is not representative of the general Danish population: Participants were selected from the two major metropolitan areas of Denmark, and are thus not representative of the entire Danish population with regard to residential noise exposure. Furthermore, only 35% of the

invited participants accepted, with participants having a higher socio-economic position compared to non-participants,[13] which may limit the generalizability of our findings. Finally, the population was aged 50-64 years at inclusion,[13] and given the long follow-up they were middle-aged or old when the study ended. It is generally acknowledged, that sleep structure changes with age, and becomes increasingly fragmented, with more awakenings and more time spend in the lighter sleep stages,[36-39] suggesting that traffic noise could be more disturbing in our study population than among a younger population. Finally, even though we were able to calculate noise exposure at both the least and most exposed facades, we did not have information on the orientation of each individual's bedroom, as well as window-opening habits.

Few other studies have previously examined the association between road traffic noise and registry-based sleep medication prescription redemption. A Finnish study found no association.[9] A Norwegian study found a borderline significant positive association, but only in the summer season and among those reporting sleeping with the windows open.[7] Unfortunately, information on window-opening habits was not available in our study, but when investigating an association between seasonal traffic noise exposure and the association with redeeming sleep medication in the summer season (June-August), we found no clear association (**Table s4**).

However, our study generally proposed a direct association only with the 10-year exposure measure, suggesting that seasonal variation may not necessarily play a large role in the present cohort. A French study found a positive association between road traffic noise and medication prescriptions only among those living in areas with low social deprivation[8]. A similar effect modification was not seen in

our study in relation to the available area-level variables: Proportion of unemployed, proportion with basic education only, and proportion with low income (**Table s5**).

While these three studies also used prescription data, the Finnish and French studies[8, 9] did not specifically investigate use of hypnotics, but included also anxiolytics and/or antidepressants, which hampers comparison with our study.

Furthermore, three European studies on road traffic noise and self-reported information on sleep medication use have been conducted; none of which found an association.[40-42] Registry-based information on medication redemption is generally assessed as more valid than self-reported information on sleep disturbance or sleep medication use, which may be more prone to information bias.

A Norwegian study suggested moderate agreement between self-reported and registry-based used of sleep medication.[43] Using registry-based information on sleep medication prescription redemption, rather than self-reported information on sleep disturbances may result in a stricter outcome-definition, which only includes the more severe, doctor-diagnosed and long-lasting cases, rather than more transient sleep problems.[44] One cohort had information on both registry-based redemption and self-reported sleep medication use,[7, 40] and interestingly they found an association between road traffic noise and redemption of registry-based prescriptions whereas no association was observed for self-reported use of sleep medication. One explanation of this seeming contradictory finding could be that the self-reported data were hampered by information bias. But the two findings are not necessarily contradictory: Registry-based data on prescriptions could reflect the more severe cases, as a prescription redemption requires a visit to and an ordination from a medical doctor[7], whereas the study on self-reported sleep medication use[40] did not specify any type of medication, and this category could therefore also include non-prescription compounds, and may thus represent milder cases of

sleep disturbance. Interestingly, the study on self-reported sleep medication use also enquired about “*difficulties falling asleep*”, “*awakenings during night*”, and “*waking up too early*”, and found a positive association between road traffic noise and all of these.[40]

Our study found a direct association between nighttime road traffic noise at the most exposed façade and sleep medication prescription redemption with 10-year exposure only. Intuitively, traffic noise may be expected to affect sleep more acutely. But as described above, the use of registry-based information on prescription redemption as an outcome captures only clinical sleep-disturbance, and in relation to this, it seems probable that a substantial amount of time is required before the sleep disturbance becomes clinical and results in redemption of a prescription for sleep medication. This should also be seen in the light of the fact that the Danish general practitioners have become more restrictive in dispensing prescriptions for sleep medication over the last decades.[45, 46]

Our analyses suggested that some subgroups of the population may be more susceptible to traffic noise exposure. Most notably, there was a strong positive association between noise exposure and sleep medication prescription redemption for men. It is generally acknowledged that women report more sleep disruption and poorer sleep quality than men,[35, 47] and that they are more prone to using sleep medication.[48-50] Explanations for this difference include hormonal factors and a higher female susceptibility to psychosocial factors in relation to sleep disturbance/disorders.[47, 51] Hence, it seems plausible that female sleep

medication use to a higher degree is a result of internal factors, and thus unrelated to traffic noise, whereas for men, external factors, including traffic noise exposure, may to a higher degree determine sleep medication use. Similarly, a positive association between traffic noise and prescription redemption was also strongest among some already high-risk subgroups of the population: Smokers and non-participants in leisure-time sports. Smoking and physical inactivity have both been found independent risk-factors for disturbed sleep,[52, 53] suggesting that these groups could be more disturbed by traffic noise. However, we would then expect to see a similar effect also among e.g. obese and those with a high intake of alcohol, as these are also established risk-factors for disturbed sleep,[54, 55] which we did not clearly see.

It has been hypothesized, that the presence of a quiet façade could compensate for the harmful effects of noise levels at the most exposed façade.[10] Few studies have previously included noise exposure at both the least and most exposed façade, as well as information on bedroom location. We identified two smaller studies on sleep disturbance in adults.[10, 11] Both found that having a bedroom facing a quiet side was associated with a lower risk of reporting sleep disturbance, but as information on noise-exposure was self-reported through questionnaires, they could be affected by exposure misclassification. A recent, larger study in Switzerland, using modelled traffic noise, found a direct association between nighttime noise level and the probability of reporting being highly disturbed by noise, with a strong effect modification by bedroom orientation, so that those with a bedroom facing the quiet side were less disturbed [12].

In our study, we found suggestions that increasing exposure at the least exposed facade seemed to entail a lower sleep medication prescription redemption in the highest exposure group. We have no a priori hypotheses for finding such an association, and it may seem counterintuitive. However, if we expect people to generally place their bedroom at the least exposed façade, one could speculate that at low noise-levels people will sleep with open windows, whereas at higher noise-levels they will sleep with closed windows. A closed window may attenuate the indoor noise-level with as much as 28 dB[56], which could entail the lowest indoor noise-level at the highest outdoor-exposure. Also, a recent Swiss study investigating modelled road traffic noise at both the most and least exposed facades in relation to mortality from myocardial infarction, found that while road traffic noise at the most exposed façade was associated with the outcome, road traffic noise at the least exposed façade attenuated the association measure, rendering the association non-significant. Interestingly, the study found this attenuation only in urban areas.[57]

The participants of the present study were chosen from the two major metropolitan areas in Denmark; Aarhus and Copenhagen. The authors of the Swiss study suggest that one would expect most people to have their bedroom at the least exposed façade and thus find a stronger association with exposure here compared to the most exposed façade, but the fact that they find the opposite in the urban areas, could be explained by more complex traffic noise exposure pictures in urban areas with more dense building configurations and road networks resulting in complex reflection patterns, which may not be adequately accounted for in the model.

Furthermore, they also proposed that masking effects of other noise sources are stronger in urban settings, and may, especially at the least exposed façade, introduce additional exposure misclassification.[57] This may also be potential explanations for the lower exposure measures between nighttime road traffic noise

exposure at the least exposed façade and sleep medication in the present study. In a nationwide Danish modelling of road traffic noise exposure, the largest difference between the least and most exposed facades of buildings was found for multistory buildings, which in Denmark often have closed courtyards with little traffic noise,[58] but potentially are highly exposed to other noise sources such as neighbors and recreational areas in the closed courtyards etc. Finally, the suggestion of an inverse association between traffic noise at the least exposed facade and sleep medication prescription redemption may also be explained by a selection of noise-sensitive persons out of dwellings with a relatively high exposure at the least exposed façade, where the bedroom is normally placed. This is, however, speculative, and cannot be examined using data from the present study.

In a sensitivity analysis, we excluded cases diagnosed with a serious illness within the last year before prescription redemption (Charlson score > 0), as this may acutely affect sleep, and entail a sleep medication prescription redemption, while at the same time a number of illnesses in the Charlson Index has been proposed associated with road traffic noise.[59-63] The fact that the sensitivity analysis finds no association in healthy individuals could suggest that our main findings may be affected by residual confounding by underlying disease. However, it also supplements our findings of an association between traffic noise and prescription redemption in already challenged sub-populations of smokers and physically inactive, by suggesting that also populations challenged by already existing disease could have their sleep more affected by nighttime traffic. This study aspect thus requires further investigation.

In conclusion, the results of the present study suggest that long-term residential exposure to nighttime road traffic noise at the most exposed façade may increase the risk of redeeming sleep medication, primarily among men, whereas for the least exposed façade, there were suggestions of an inverse association, however with no clear trends across exposure-groups. For noise at the most exposed façade, the association seemed strongest among already high-risk sub-populations of smokers and physically inactive. The present study contributes to the relatively limited literature on traffic noise and sleep medication prescription redemption, indicating that long-term traffic noise exposure at the most exposed façade could be associated with more severe sleep disturbances, especially in men and high-risk populations. However, further studies are required, especially with regards to potentially differing associations in subgroups of the population.

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References

1. World Health Organization: Night Noise Guidelines for Europe. Copenhagen: World Health Organization; 2009.
2. World Health Organization: Burden of disease from environmental noise. Quantification of healthy life years lost in Europe. The WHO European Centre for Environment and Health, Bonn Office, WHO Regional Office for Europe; 2011.
3. Pirrera S, De Valck E, Cluydts R: Nocturnal road traffic noise: A review on its assessment and consequences on sleep and health. *Environment international* 2010, 36(5):492-498.
4. Miedema HM, Vos H: Associations between self-reported sleep disturbance and environmental noise based on reanalyses of pooled data from 24 studies. *Behavioral sleep medicine* 2007, 5(1):1-20.
5. Basner M, McGuire S: WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Effects on Sleep. *International journal of environmental research and public health* 2018, 15(3).
6. Bodin T, Bjork J, Ohrstrom E, Ardo J, Albin M: Survey context and question wording affects self reported annoyance due to road traffic noise: a comparison between two cross-sectional studies. *Environmental health : a global access science source* 2012, 11(1):14.
7. Evandt J, Oftedal B, Krog NH, Skurtveit S, Nafstad P, Schwarze PE, Skovlund E, Houthuijs D, Aasvang GM: Road traffic noise and registry based use of sleep medication. *Environmental health : a global access science source* 2017, 16(1):110.
8. Bocquier A, Cortaredona S, Boutin C, David A, Bigot A, Sciortino V, Nauleau S, Gaudart J, Giorgi R, Verger P: Is exposure to night-time traffic noise a risk factor for purchase of anxiolytic-hypnotic medication? A cohort study. *Eur J Public Health* 2014, 24(2):298-303.
9. Halonen JJ, Lanki T, Yli-Tuomi T, Turunen AW, Pentti J, Kivimaki M, Vahtera J: Associations of traffic noise with self-rated health and psychotropic medication use. *Scandinavian journal of work, environment & health* 2014, 40(3):235-243.
10. Bodin T, Bjork J, Ardo J, Albin M: Annoyance, sleep and concentration problems due to combined traffic noise and the benefit of quiet side. *International journal of environmental research and public health* 2015, 12(2):1612-1628.
11. Van Renterghem T, Botteldooren D: Focused study on the quiet side effect in dwellings highly exposed to road traffic noise. *International journal of environmental research and public health* 2012, 9(12):4292-4310.
12. Brink M, Schaffer B, Vienneau D, Pieren R, Foraster M, Eze IC, Rudzik F, Thiesse L, Cajochen C, Probst-Hensch N *et al*: Self-Reported Sleep Disturbance from Road, Rail and Aircraft Noise: Exposure-Response Relationships and Effect Modifiers in the SiRENE

- Study. *International journal of environmental research and public health* 2019, 16(21).
13. Tjønneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, Overvad K: Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. *Scandinavian journal of public health* 2007, 35(4):432-441.
 14. Pedersen CB: The Danish Civil Registration System. *Scandinavian journal of public health* 2011, 39(7 Suppl):22-25.
 15. Bendtsen H: The Nordic prediction Method for Road Traffic Noise. *SciTotalEnviron* 1999, 235:331-338.
 16. Christensen G: The Building and Housing Register. *Scandinavian journal of public health* 2011, 39(7 Suppl):106-108.
 17. GeoDanmark: Geodanmark. Fællesoffentligt Geografisk Administrationsgrundlag (FOT) Danmark. Copenhagen; 2012.
 18. Jensen SS, Hillig K: GIS-based National Road and Traffic Database 1960-2020. In., vol. 151: Aarhus University, DCE – Danish Centre for Environment and Energy; 2019: 24.
 19. Kildemoes HW, Sørensen HT, Hallas J: The Danish National Prescription Registry. *Scandinavian journal of public health* 2011, 39(7 Suppl):38-41.
 20. WHO Collaborating Centre for Drug Statistics Methodology: Guidelines for ATC Classification and DDD Assignment 2013. Oslo; 2012.
 21. Hvidtfeldt UA, Sørensen M, Geels C, Ketzel M, Khan J, Tjønneland A, Overvad K, Brandt J, Raaschou-Nielsen O: Long-term residential exposure to PM_{2.5}, PM₁₀, black carbon, NO₂, and ozone and mortality in a Danish cohort. *Environment International* 2019, 123:265-272.
 22. Christensen JS, Raaschou-Nielsen O, Tjønneland A, Nordsborg RB, Jensen SS, Sørensen TI, Sørensen M: Long-term exposure to residential traffic noise and changes in body weight and waist circumference: A cohort study. *Environmental research* 2015, 143(Pt A):154-161.
 23. Christensen JS, Raaschou-Nielsen O, Tjønneland A, Overvad K, Nordsborg RB, Ketzel M, Sørensen T, Sørensen M: Road Traffic and Railway Noise Exposures and Adiposity in Adults: A Cross-Sectional Analysis of the Danish Diet, Cancer, and Health Cohort. *Environmental Health Perspectives* 2016, 124(3):329-335.
 24. Pyko A, Eriksson C, Oftedal B, Hilding A, Ostenson CG, Krog NH, Julin B, Aasvang GM, Pershagen G: Exposure to traffic noise and markers of obesity. *Occupational and Environmental Medicine* 2015, 72(8):594-601.
 25. Roswall N, Christensen JS, Bidstrup PE, Raaschou-Nielsen O, Jensen SS, Tjønneland A, Sørensen M: Associations between residential traffic noise exposure and smoking habits and alcohol consumption-A population-based study. *Environ Pollut* 2018, 236:983-991.
 26. Roswall N, Ammitzboll G, Christensen JS, Raaschou-Nielsen O, Jensen SS, Tjønneland A, Sørensen M: Residential exposure to traffic

- noise and leisure-time sports - A population-based study. *International journal of hygiene and environmental health* 2017, 220(6):1006-1013
27. Foraster M, Eze IC, Vienneau D, Brink M, Cajochen C, Caviezel S, Heritier H, Schaffner E, Schindler C, Wanner M *et al*: Long-term transportation noise annoyance is associated with subsequent lower levels of physical activity. *Environment International* 2016, 91:341-349.
 28. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases* 1987, 40(5):373-383.
 29. Lynge E, Sandegaard JL, Rebolj M: The Danish National Patient Register. *Scandinavian journal of public health* 2011, 39(7 Suppl):30-33.
 30. Therneau T: Spline terms in a Cox model. <https://cran.r-project.org/web/packages/survival/vignettes/splines.pdf>; 2019: 1-10.
 31. World Health Organization: Environmental Noise Guidelines for the European Region. Edited by World Health Organization. Copenhagen; 2018.
 32. Rasmussen L, Valentin J, Gesser KM, Hallas J, Pottegard A: Validity of the Prescriber Information in the Danish National Prescription Registry. *Basic Clin Pharmacol Toxicol* 2016, 119(4):376-380.
 33. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M: Data Resource Profile: The Danish National Prescription Registry. *International journal of epidemiology* 2017, 46(3):798-798f.
 34. Ström T: Road traffic noise - an estimate of prediction uncertainty (in Swedish), vol. 24: Swedish National Testing and Research Institute 1997.
 35. Sundhedsstyrelsen: Danskernes Sundhed - Den nationale Sundhedsprofil 2017. 1. edn. København; 2018.
 36. Leger D, Guilleminault C, Dreyfus JP, Delahaye C, Paillard M: Prevalence of insomnia in a survey of 12,778 adults in France. *J Sleep Res* 2000, 9(1):35-42.
 37. Sateia MJ, Doghramji K, Hauri PJ, Morin CM: Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep* 2000, 23(2):243-308.
 38. Cooke JR, Ancoli-Israel S: Normal and abnormal sleep in the elderly. *Handb Clin Neurol* 2011, 98:653-665.
 39. Wolkove N, Elkholy O, Baltzan M, Palayew M: Sleep and aging: 1. Sleep disorders commonly found in older people. *CMAJ* 2007, 176(9):1299-1304.
 40. Evandt J, Oftedal B, Hjertager Krog N, Nafstad P, Schwarze PE, Marit Aasvang G: A Population-Based Study on Nighttime Road Traffic Noise and Insomnia. *Sleep* 2017, 40(2).
 41. de Kluizenaar Y, Janssen SA, van Lenthe FJ, Miedema HM, Mackenbach JP: Long-term road traffic noise exposure is associated with an increase in morning tiredness. *The Journal of the Acoustical Society of America* 2009, 126(2):626-633.

42. Floud S, Vigna-Taglianti F, Hansell A, Blangiardo M, Houthuijs D, Breugelmans O, Cadum E, Babisch W, Selander J, Pershagen G *et al*: Medication use in relation to noise from aircraft and road traffic in six European countries: results of the HYENA study. *Occupational and environmental medicine* 2011, 68(7):518-524.
43. Evandt J, Skurtveit S, Oftedal B, Krog NH, Nafstad P, Skovlund E, Schwarze PE, Aasvang GM: Agreement between self-reported and registry-based use of sleep medications and tranquilizers. *Pharmacoepidemiol Drug Saf* 2019.
44. Barregard L, Stansfeld S: Medication use as an outcome variable in environmental (noise) epidemiology. *Scandinavian journal of work, environment & health* 2014, 40(3):211-213.
45. Statens Serum Institut: Fup og fakta om danskernes brug af sovemedicin og beroligende midler. København: Sundhedsdatastyrelsen; 2012: 8.
46. Sundhedsdatastyrelsen: Stadig færre langtidsbrugere af sovemedicin og angstdæmpende medicin. 2018: 11.
47. Mong JA, Cusmano DM: Sex differences in sleep: impact of biological sex and sex steroids. *Philos Trans R Soc Lond B Biol Sci* 2016, 371(1688):20150110.
48. Schlack R, Hapke U, Maske U, Busch M, Cohrs S: [Frequency and distribution of sleep problems and insomnia in the adult population in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2013, 56(5-6):740-748.
49. Bertisch SM, Herzig SJ, Winkelman JW, Buettner C: National use of prescription medications for insomnia: NHANES 1999-2010. *Sleep* 2014, 37(2):343-349.
50. Kodaira K, Silva MT: Sleeping pill use in Brazil: a population-based, cross-sectional study. *BMJ Open* 2017, 7(7):e016233.
51. Mallampalli MP, Carter CL: Exploring sex and gender differences in sleep health: a Society for Women's Health Research Report. *J Womens Health (Larchmt)* 2014, 23(7):553-562.
52. Kovacevic A, Mavros Y, Heisz JJ, Fiatarone Singh MA: The effect of resistance exercise on sleep: A systematic review of randomized controlled trials. *Sleep medicine reviews* 2018, 39:52-68.
53. Deleanu OC, Pocora D, Mihalcuta S, Ulmeanu R, Zaharie AM, Mihaltan FD: Influence of smoking on sleep and obstructive sleep apnea syndrome. *Pneumologia* 2016, 65(1):28-35.
54. Xanthopoulos MS, Berkowitz RI, Tapia IE: Effects of obesity therapies on sleep disorders. *Metabolism* 2018, 84:109-117.
55. Garcia AN, Salloum IM: Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: A focused review. *Am J Addict* 2015, 24(7):590-598.
56. Locher B, Piquerez A, Habermacher M, Ragettli M, Roosli M, Brink M, Cajochen C, Vienneau D, Foraster M, Muller U *et al*: Differences between Outdoor and Indoor Sound Levels for Open, Tilted, and Closed Windows. *International journal of environmental research and public health* 2018, 15(1).

57. Vienneau D, Heritier H, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Kopfli M, Pieren R *et al*: Facades, floors and maps - Influence of exposure measurement error on the association between transportation noise and myocardial infarction. *Environment international* 2019, 123:399-406.
58. Thatcher J, Poulsen AH, Raaschou-Nielsen O, Jensen AR, Hillig K, Roswall N, Hvidtfeldt UA, Jensen SS, Levin G, Alvear VHV *et al*: Danish National Road Traffic Noise Exposure: An overview. 2019 Dec 19;182:109051. doi: 10.1016/j.envres.2019.109051. [Epub ahead of print]
59. Kempen EV, Casas M, Pershagen G, Foraster M: WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Cardiovascular and Metabolic Effects: A Summary. *International journal of environmental research and public health* 2018, 15(2).
60. Sorensen M, Ketzel M, Overvad K, Tjonneland A, Raaschou-Nielsen O: Exposure to road traffic and railway noise and postmenopausal breast cancer: A cohort study. *International journal of cancer* 2014, 134(11):2691-2698.
61. Andersen ZJ, Jorgensen JT, Elsborg L, Lophaven SN, Backalarz C, Laursen JE, Pedersen TH, Simonsen MK, Brauner EV, Lynge E: Long-term exposure to road traffic noise and incidence of breast cancer: a cohort study. *Breast Cancer Res* 2018, 20(1):119.
62. Roswall N, Raaschou-Nielsen O, Ketzel M, Overvad K, Halkjaer J, Sorensen M: Modeled traffic noise at the residence and colorectal cancer incidence: a cohort study. *Cancer causes & control* 2017, 28(7):745-753.
63. Sorensen M, Harbo Poulsen A, Ketzel M, Oksbjerg Dalton S, Friis S, Raaschou-Nielsen O: Residential exposure to traffic noise and risk for non-hodgkin lymphoma among adults. *Environmental research* 2015, 142:61-65.

Tables

Table 1: Baseline characteristics of the Diet, Cancer and Health cohort according to road traffic noise exposure at the most exposed façade at baseline^a

	Total cohort	L_n ≤ 45 dB	L_n >45-≤50 dB	L_n >50-≤55 dB	L_n > 55 dB
	N = 44,438	N = 15,406	N = 11,116	N = 9,552	N = 8,364
Nighttime road traffic noise, most exposed façade, dB	48.0 (36.0-61.1)	41.2 (32.7-44.7)	47.4 (45.3-49.8)	52.2 (50.3-54.7)	58.6 (55.3-65.5)
Nighttime road traffic noise, least exposed façade, dB	39.8 (30.4-50.1)	36.4 (28.2-42.6)	42.8 (32.7-47.6)	43.0 (32.5-51.0)	41.9 (32.8-54.4)
Female, %	50.7	49.1	50.8	51.9	52.0
Age at baseline, years	57.3 (51.7-65.5)	57.1 (51.5-65.4)	57.3 (51.7-65.3)	57.6 (51.8-65.6)	57.6 (52.0-65.8)
Follow-up time, years	18.5 (1.7-18.5)	18.5 (1.8-18.5)	18.5 (1.8-18.5)	18.5 (1.7-18.5)	18.5 (1.6-18.5)
Household income, %					
1 st quintile	4.0	2.8	3.5	4.9	6.2
2 nd quintile	10.5	7.9	9.7	12.3	14.1
3 rd quintile	13.0	11.3	12.8	13.9	15.4
4 th quintile	22.1	20.9	21.9	22.6	23.8
5 th quintile	50.4	57.2	52.1	46.3	40.4
Education, %					
Basic	27.2	24.4	26.6	29.4	30.6
Vocational	46.1	45.4	46.6	45.7	47.5
Higher	26.7	30.3	26.8	24.9	22.0
Cohabiting, %	73.0	78.9	73.9	68.6	66.0
Area-level ^b percentage of:					
Persons with low income, %	9 (4-25)	8 (4-21)	9 (4-23)	10 (4-29)	11 (3-29)
Persons with basic education, %	24 (12-38)	24 (11-35)	26 (12-38)	25 (13-38)	24 (12-38)
Persons unemployed, %	6 (4-11)	5 (3-9)	6 (4-11)	6 (4-12)	7 (4-13)
Smoking status, %					
Never	36.6	38.5	38.1	35.1	32.9
Former	28.1	29.5	27.5	27.5	27.0
Current	35.3	32.0	34.3	37.4	40.1
Alcohol, g/day ^c	13.3 (1.2-64.0)	13.3 (1.2-61.2)	13.5 (1.2-63.3)	13.0 (1.0-65.2)	13.5 (1.0-68.5)
Abstainers, %	2.0	1.6	2.1	2.2	2.3
Leisure-time physical activity	54.4	57.1	55.6	52.7	49.5
^a Median and 5-95 percentile, unless otherwise stated.					
^b By parish					
^c Among those drinking alcohol					

Table 2. Crude and adjusted associations between nighttime residential road traffic noise exposure (L_n) at the most exposed façade and sleep medication prescription redemption.			
	Cases	Model 1^a HR (95% CI)	Model 2^b HR (95% CI)
Average L_n 1 year before prescription redemption			
≤ 45 dB	3,532	1.00 (ref.)	1.00 (ref.)
$>45\text{--}\leq 50$ dB	3,516	1.00 (0.95-1.04)	1.00 (0.95-1.05)
$>50\text{--}\leq 55$ dB	3,402	1.02 (0.98-1.07)	1.03 (0.98-1.08)
>55 dB	2,664	1.01 (0.96-1.06)	1.01 (0.96-1.06)
Average L_n 5 years before prescription redemption			
≤ 45 dB	3,413	1.00 (ref.)	1.00 (ref.)
$>45\text{--}\leq 50$ dB	3,531	1.00 (0.95-1.04)	1.00 (0.95-1.05)
$>50\text{--}\leq 55$ dB	3,478	1.02 (0.98-1.07)	1.03 (0.98-1.08)
>55 dB	2,692	1.01 (0.96-1.06)	1.01 (0.96-1.06)
Average L_n 10 years before prescription redemption			
≤ 45 dB	3,270	1.00 (ref.)	1.00 (ref.)
$>45\text{--}\leq 50$ dB	3,583	1.02 (0.97-1.07)	1.02 (0.98-1.07)
$>50\text{--}\leq 55$ dB	3,536	1.03 (0.98-1.08)	1.03 (0.99-1.08)
>55 dB	2,725	1.05 (1.00-1.10)	1.05 (1.00-1.10)
^a Adjusted for age (by design), calendar year and sex			
^b Adjusted as model 1, and additionally for educational level (basic, vocational, higher), disposable income (in quintiles), cohabitation status (married/registered partnership, and other), proportion of inhabitants with low disposable income (parish level), proportion of inhabitants with only basic education (parish level), proportion of inhabitants being unemployed (parish level)			

Table 3. Crude and adjusted associations between nighttime residential road traffic noise exposure (L_n) at the least exposed façade and sleep medication prescription redemption.			
	Cases	Model 1^a HR (95% CI)	Model 2^b HR (95% CI)
Average L_n 1 year before prescription redemption			
≤ 35 dB	2,362	1.00 (ref.)	1.00 (ref.)
$>35\text{--}\leq 40$ dB	3,847	1.00 (0.96-1.05)	1.00 (0.96-1.05)
$>40\text{--}\leq 45$ dB	3,829	1.00 (0.95-1.04)	1.01 (0.96-1.06)
>45 dB	3,062	0.93 (0.89-0.98)	0.95 (0.90-1.00)
Average L_n 5 years before prescription redemption			
≤ 35 dB	2,220	1.00 (ref.)	1.00 (ref.)
$>35\text{--}\leq 40$ dB	3,948	1.02 (0.98-1.08)	1.02 (0.97-1.07)
$>40\text{--}\leq 45$ dB	3,949	1.02 (0.97-1.07)	1.03 (0.98-1.09)
>45 dB	2,997	0.94 (0.90-0.99)	0.96 (0.91-1.01)
Average L_n 10 years before prescription redemption			
≤ 35 dB	2,077	1.00 (ref.)	1.00 (ref.)
$>35\text{--}\leq 40$ dB	4,048	1.01 (0.97-1.07)	1.01 (0.96-1.06)
$>40\text{--}\leq 45$ dB	4,052	1.00 (0.95-1.05)	1.01 (0.96-1.07)
>45 dB	2,937	0.98 (0.93-1.03)	1.00 (0.95-1.05)
^a Adjusted for age (by design), calendar year and sex			
^b Adjusted as model 1, and additionally for educational level (basic, vocational, higher), disposable income (in quintiles), cohabitation status (married/registered partnership, and other), proportion of inhabitants with low disposable income (parish level), proportion of inhabitants with only basic education (parish level), and proportion of inhabitants being unemployed (parish level)			

Table 4. Modification of the association between nighttime road traffic noise at the most exposed façade (L_n) by sex, lifestyle-factors, cohabitation and education.

		Average L_n 1 year before prescription redemption	Average L_n 5 years before prescription redemption	Average L_n 10 years before prescription redemption		Average L_n 1 year before prescription redemption	Average L_n 5 years before prescription redemption	Average L_n 10 years before prescription redemption
	N Cases	HR (95% CI) ^a	HR (95% CI) ^a	HR (95% CI) ^a	N Cases	HR (95% CI) ^a	HR (95% CI) ^a	HR (95% CI) ^a
Sex	Male				Female			
≤ 45 dB	1,456	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,814	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
$>45-\leq 50$ dB	1,512	1.01 (0.94-1.09)	1.04 (0.97-1.11)	1.05 (0.98-1.13)	2,071	0.99 (0.93-1.05)	0.99 (0.93-1.05)	1.00 (0.94-1.06)
$>50-\leq 55$ dB	1,457	1.06 (0.98-1.13)	1.05 (0.97-1.12)	1.07 (0.99-1.15)	2,079	1.00 (0.94-1.08)	1.01 (0.95-1.07)	1.01 (0.95-1.07)
>55 dB	1,188	1.08 (1.00-1.16)	1.11 (1.03-1.120)	1.16 (1.08-1.25)	1,537	0.96 (0.90-1.02)	0.95 (0.89-1.01)	0.97 (0.91-1.04)
Obese^b	Yes				No			
≤ 45 dB	429	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	2,840	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
$>45-\leq 50$ dB	493	0.99 (0.87-1.11)	1.01 (0.90-1.15)	1.02 (0.92-1.18)	3,083	1.00 (0.95-1.05)	1.01 (0.96-1.06)	1.02 (0.97-1.07)
$>50-\leq 55$ dB	552	1.07 (0.95-1.21)	1.07 (0.95-1.20)	1.06 (0.94-1.20)	2,978	1.02 (0.97-1.07)	1.02 (0.97-1.07)	1.03 (0.98-1.08)
>55 dB	432	1.01 (0.89-1.15)	1.02 (0.89-1.16)	1.02 (0.90-1.16)	2,289	1.00 (0.95-1.06)	1.01 (0.96-1.07)	1.06 (1.00-1.11)
Smoking	Ever				Never			
≤ 45 dB	3,438	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,205	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
$>45-\leq 50$ dB	2,311	1.02 (0.96-1.08)	1.03 (0.97-1.09)	1.03 (0.97-1.09)	1,272	0.97 (0.90-1.05)	0.98 (0.91-1.06)	1.01 (0.94-1.09)
$>50-\leq 55$ dB	2,404	1.05 (0.99-1.11)	1.05 (1.00-1.12)	1.07 (1.01-1.14)	1,132	0.98 (0.91-1.06)	0.97 (0.89-1.05)	0.95 (0.88-1.03)
>55 dB	1,920	1.03 (0.97-1.09)	1.04 (0.98-1.11)	1.08 (1.02-1.15)	805	0.96 (0.88-1.04)	0.95 (0.87-1.04)	0.98 (0.89-1.07)
Alcohol	> recommendations				\leq recommendations^c			
≤ 45 dB	1,403	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,205	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
$>45-\leq 50$ dB	1,507	0.96 (0.89-1.03)	0.95 (0.89-1.02)	0.98 (0.91-1.05)	2,076	1.03 (0.97-1.09)	1.05 (0.99-1.11)	1.05 (0.99-1.12)
$>50-\leq 55$ dB	1,477	1.02 (0.95-1.09)	1.01 (0.94-1.08)	1.03 (0.95-1.10)	2,059	1.03 (0.97-1.10)	1.04 (0.98-1.10)	1.04 (0.98-1.11)
>55 dB	1,204	0.97 (0.90-1.04)	0.99 (0.92-1.07)	1.03 (0.95-1.11)	1,521	1.03 (0.97-1.10)	1.03 (0.96-1.10)	1.06 (0.99-1.13)

Leisure-time sports	No				Yes			
≤ 45 dB	1,350	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,920	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
$>45\text{--}\leq 50$ dB	1,583	1.07 (1.00-1.15)	1.10 (1.02-1.17)	1.13 (1.05-1.21)	2,000	0.95 (0.89-1.01)	0.95 (0.89-1.01)	0.95 (0.89-1.01)
$>50\text{--}\leq 55$ dB	1,644	1.04 (0.97-1.12)	1.04 (0.97-1.12)	1.05 (0.98-1.13)	1,892	1.01 (0.95-1.08)	1.01 (0.95-1.08)	1.02 (0.96-1.09)
>55 dB	1,384	1.07 (1.00-1.15)	1.08 (1.01-1.17)	1.12 (1.04-1.20)	1,341	0.95 (0.89-1.02)	0.96 (0.89-1.02)	0.99 (0.93-1.07)
Cohabiting	No				Yes			
≤ 45 dB	632	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	2,638	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
$>45\text{--}\leq 50$ dB	953	1.00 (0.91-1.09)	0.99 (0.91-1.09)	1.07 (0.98-1.18)	2,630	1.00 (0.95-1.06)	1.02 (0.96-1.07)	1.01 (0.96-1.06)
$>50\text{--}\leq 55$ dB	1,146	1.06 (0.97-1.15)	1.07 (0.98-1.17)	1.12 (1.02-1.22)	2,390	1.01 (0.96-1.07)	1.01 (0.96-1.05)	1.01 (0.95-1.06)
>55 dB	982	1.01 (0.92-1.11)	1.01 (0.92-1.11)	1.07 (0.98-1.18)	1,743	1.01 (0.95-1.07)	1.02 (0.96-1.08)	1.05 (0.99-1.11)
Education	Low				Medium/high			
≤ 45 dB	804	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	2,465	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
$>45\text{--}\leq 50$ dB	1,001	1.00 (0.91-1.09)	1.04 (0.95-1.13)	1.04 (0.95-1.14)	2,575	1.00 (0.95-1.05)	1.00 (0.95-1.06)	1.02 (0.96-1.07)
$>50\text{--}\leq 55$ dB	1,074	1.04 (0.95-1.13)	1.03 (0.94-1.12)	1.02 (0.93-1.11)	2,456	1.02 (0.97-1.08)	1.02 (0.97-1.08)	1.04 (0.99-1.10)
>55 dB	869	1.07 (0.97-1.17)	1.06 (0.96-1.16)	1.08 (0.98-1.18)	1,852	0.98 (0.92-1.04)	1.00 (0.94-1.06)	1.04 (0.98-1.10)

^a Adjusted for age (by design), calendar year, sex, proportion of inhabitants with low disposable income (parish level), proportion of inhabitants with only basic education (parish level), proportion of inhabitants being unemployed (parish level), educational level (basic, vocational, higher), disposable income (in quintiles), cohabitation status (married/registered partnership, and other)

^b BMI ≥ 30 kg/m²

^c The Danish Health Authority recommends no more than 7 units (in Denmark defined as 12 g alcohol) per week for women and 14 units for men

Table 5. Modification of the association between nighttime road traffic noise at the least exposed façade (L_n) by sex, lifestyle-factors, cohabitation, and education.

		Average L_n 1 year before prescription redemption	Average L_n 5 years before prescription redemption	Average L_n 10 years before prescription redemption		Average L_n 1 year before prescription redemption	Average L_n 5 years before prescription redemption	Average L_n 10 years before prescription redemption
	N Cases	HR (95% CI) ^a	HR (95% CI) ^a	HR (95% CI) ^a	N Cases	HR (95% CI) ^a	HR (95% CI) ^a	HR (95% CI) ^a
Sex	Male				Female			
≤ 35 dB	924	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,153	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>35 - ≤ 40 dB	1,811	1.06 (0.98-1.14)	1.07 (0.99-1.15)	1.08 (1.00-1.16)	2,237	0.96 (0.90-1.02)	0.99 (0.93-1.06)	0.96 (0.90-1.03)
>40 - ≤ 45 dB	1,666	1.02 (0.94-1.09)	1.03 (0.95-1.11)	1.03 (0.95-1.11)	2,386	1.00 (0.93-1.06)	1.03 (0.96-1.10)	1.00 (0.94-1.07)
>45 dB	1,212	1.00 (0.92-1.08)	1.01 (0.93-1.09)	1.05 (0.97-1.14)	1,725	0.92 (0.86-0.99)	0.93 (0.86-0.99)	0.96 (0.90-1.03)
Obese^b	Yes				No			
≤ 35 dB	282	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,795	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>35 - ≤ 40 dB	558	0.99 (0.97-1.12)	1.08 (0.94-1.23)	1.06 (0.92-1.21)	3,487	1.00 (0.95-1.06)	1.01 (0.96-1.07)	1.01 (0.95-1.06)
>40 - ≤ 45 dB	593	1.01 (0.89-1.15)	1.09 (0.96-1.25)	1.05 (0.92-1.21)	3,450	1.00 (0.95-1.06)	1.02 (0.97-1.08)	1.01 (0.95-1.06)
>45 dB	473	0.98 (0.86-1.12)	1.04 (0.95-1.19)	1.04 (0.91-1.20)	2,458	0.94 (0.89-1.00)	0.95 (0.90-1.00)	0.99 (0.93-1.05)
Smoking	Ever				Never			
≤ 35 dB	1,366	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	711	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>35 - ≤ 40 dB	2,747	1.00 (0.94-1.05)	1.02 (0.96-1.08)	1.02 (0.96-1.08)	1,301	1.02 (0.93-1.10)	1.02 (0.94-1.11)	1.00 (0.91-1.09)
>40 - ≤ 45 dB	2,630	1.00 (0.95-1.07)	1.04 (0.98-1.10)	1.02 (0.96-1.08)	1,422	1.03 (0.94-1.11)	1.04 (0.95-1.13)	1.02 (0.94-1.11)
>45 dB	1,957	0.97 (0.91-1.03)	0.98 (0.92-1.04)	1.01 (0.95-1.08)	980	0.93 (0.85-1.02)	0.94 (0.85-1.02)	0.97 (0.89-1.06)
Alcohol	> recommendations				\leq recommendations^c			

≤ 35 dB	906	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,1 71	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>35 - ≤ 40 dB	1,7 26	0.98 (0.91- 1.05)	1.00 (0.93- 1.08)	1.01 (0.94- 1.09)	2,3 22	1.02 (0.96- 1.08)	1.04 (0.98- 1.11)	1.01 (0.95- 1.08)
>40 - ≤ 45 dB	1,7 19	0.90 (0.84- 0.97)	0.93 (0.86- 1.00)	0.95 (0.81- 0.99)	2,3 33	1.08 (1.01- 1.15)	1.11 (1.04- 1.18)	1.08 (1.01- 1.16)
>45 dB	1,2 40	0.91 (0.84- 0.99)	0.91 (0.84- 0.98)	0.96 (0.88- 1.03)	1,6 97	0.97 (0.90- 1.04)	0.99 (0.92- 1.06)	1.02 (0.95- 1.09)
Leisure-time sports	No				Yes			
≤ 35 dB	902	1.00	1.00 (ref.)	1.00 (ref.)	1,1 75	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>35 - ≤ 40 dB	1,8 56	1.01 (0.94- 1.08)	1.04 (0.97- 1.12)	1.03 (0.96- 1.11)	2,1 92	1.00 (0.94- 1.07)	1.01 (0.95- 1.08)	1.00 (0.94- 1.07)
>40 - ≤ 45 dB	1,8 36	1.06 (0.99- 1.14)	1.09 (1.02- 1.18)	1.06 (0.98- 1.14)	2,2 16	0.96 (0.90- 1.03)	0.99 (0.92- 1.05)	0.98 (0.91- 1.05)
>45 dB	1,3 67	1.01 (0.94- 1.10)	1.03 (0.95- 1.11)	1.06 (0.98- 1.14)	1,5 70	0.90 (0.84- 0.97)	0.91 (0.85- 0.98)	0.96 (0.89- 1.07)
Cohabiting	No				Yes			
≤ 35 dB	486	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,5 91	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>35 - ≤ 40 dB	1,1 38	0.97 (0.88- 1.06)	1.03 (0.94- 1.13)	1.00 (0.90- 1.10)	2,9 10	1.02 (0.96- 1.07)	1.02 (0.97- 1.08)	1.02 (0.96- 1.08)
>40 - ≤ 45 dB	1,1 83	0.98 (0.89- 1.07)	1.01 (0.92- 1.12)	1.02 (0.92- 1.12)	2,8 69	1.02 (0.96- 1.08)	1.04 (0.98- 1.10)	1.01 (0.96- 1.07)
>45 dB	906	0.95 (0.86- 1.05)	0.98 (0.88- 1.08)	1.01 (0.91- 1.12)	2,0 31	0.95 (0.89- 1.01)	0.96 (0.91- 1.02)	0.99 (0.93- 1.07)
Education	Low				Medium/high			
≤ 35 dB	579	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1,4 98	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>35 - ≤ 40 dB	1,0 89	1.02 (0.93- 1.11)	1.04 (0.95- 1.14)	1.02 (0.93- 1.12)	2,9 56	1.00 (0.94- 1.05)	1.02 (0.96- 1.08)	1.01 (0.95- 1.07)
>40 - ≤ 45 dB	1,1 70	1.03 (0.93- 1.12)	1.05 (0.96- 1.15)	1.05 (0.95- 1.15)	2,8 73	1.00 (0.94- 1.06)	1.03 (0.97- 1.09)	1.00 (0.94- 1.06)
>45 dB	910	1.00 (0.91- 1.10)	1.00 (0.91- 1.10)	1.02 (0.92- 1.12)	2,0 21	0.93 (0.88- 0.99)	0.94 (0.89- 1.01)	0.99 (0.93- 1.05)

^a Adjusted for age (by design), calendar year, sex, proportion of inhabitants with low disposable income (parish level), proportion of inhabitants with only basic education

(parish level), proportion of inhabitants being unemployed (parish level), educational level (basic, vocational, higher), disposable income (in quintiles), cohabitation status (married/registered partnership, and other)

^b BMI ≥ 30 kg/m²

^c The Danish Health Authority recommends no more than 7 units (defined as 12 g alcohol) per week for women and 14 units for men

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